CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
1-(3-Chloroallyl)-3,5,7-Triaza-1-Azoniaadamantane Chloride

Chemical Code # 000250, Tolerance # 50276
SB 950 # 305

Original date: March 26, 2003

I. DATA GAP STATUS

Chronic rat:	Data gap, no study on file.
Subchronic, rat, oral	Unacceptable studies, no adverse effect indicated
Chronic non-rodent:	Data gap, no study on file.
Subchronic, dog, oral	Unacceptable study, no adverse effect indicated
Subchronic, rabbit, dermal	Acceptable study, no adverse effect
Oncogenicity, rat:	Data gap, no study on file.
Oncogenicity, mouse:	Data gap, no study on file.
Subchronic, mouse, dermal	Unacceptable study, possible adverse systemic effect (based on preliminary data)
Reproduction rat:	Data gap, no study on file.
Teratology, rat:	No data gap, possible adverse effect indicated
Teratology, rabbit:	Data gap, no study on file.
Gene mutation:	No data gap, possible adverse effect .
Chromosome:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect .
Neurotoxicity:	Not required at this time

Note, Toxicology one-liners are attached.
All record numbers through 202567 were examined.
** indicates acceptable study
Boldface indicates possible adverse effect
File name: T030326
Original : J. Kishiyama and Gee, March 26, 2003
In April, 1995, US EPA issued a Reregistration Eligibility Decision (RED) for “Dowicil®CTAC” including data requirements. CTAC is an antimicrobial with non-food uses. All data required to fulfill Tier 1 have been submitted and the data requirements fulfilled by US EPA.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC TOXICITY, RAT (and others)

No study submitted.

Subchronic, rat

007 038057 Humiston, C. G., S. B. McCollister, C. E. Wade and R. J. Kociba "Dowicil® 100 - Antimicrobial agent - results of a 90-day dietary feeding study in rats." (Dow Chemical, July 21, 1972) Dowicil 100 (91.4% active ingredient, lot no. 188718) was fed in the diet for 90 days to give doses of 0, 7.5, 15, 30 or 60 mg/kg/day to Sprague-Dawley rats, 10/sex/dose. The concentrations in the diet were adjusted to maintain the doses. Limited hematology, clinical chemistry and urinalysis were conducted on 5/sex/dose. Organ weights for heart, liver, kidney, testes and brain were recorded. Limited list of tissues were examined for 5/sex in the controls and high dose groups except the livers of 5 males were examined for the lower doses. There was no mortality. Body weights were significantly lower in all treated groups and was related to lower food intake, especially early in the study and more so for males. The lower intake was thought to be due to a palatability problem. The only histological finding was minimal hepatocellular swelling in 3/5 males at 60 mg/kg/day compared with 0/5 in controls. This finding was not seen in female rats. NOEL apparently 30 mg/kg/day for effects other than body weight, for which the NOEL < 7.5 mg/kg/day. UNACCEPTABLE. Not upgradeable. No adverse effect identified. No worksheet. (Gee, 3/24/03).

007 038058 Humiston, C. G., C. E. Wade and R. J. Kociba "Dowicil® 100 antimicrobial agent - results of a supplemental 90-day dietary feeding study in rats." (Dow Chemical, December 13, 1972) Dowicil 100 (lot 188718, 91.4% active ingredient) was fed in the diet at 0, 1, 2 or 4 mg/kg/day in order to find a dose in the diet acceptable to rats. There were 10 Sprague-Dawley rats per sex per dose. No clinical studies were conducted as those in the previous study (record 038057) were negative. Body weights were depressed with males (approximately 6 - 7% lower) at 4 mg/kg/day with 2 mg/kg/day being comparable to controls. Food consumption was lower at 4 mg/kg/day for males but not females. Limited tissues were preserved but not examined histologically, based on the previous study. NOEL = 2 mg/kg/day (body weight in males) UNACCEPTABLE, not upgradeable. No adverse effects. No worksheet. (Gee, 3/24/03)

-003 16321 Duplicate of 038058

Subchronic, Rabbit and Mouse.

** 008 068708 Corley, R. A., F. S. Cieszlak and G. C. Jersey. "Cis/Trans-CTAC: 13-Week Dermal Toxicity Study in New Zealand White Rabbits." (Dow Chemical, Laboratory Project Study ID: K27342-061, June 8, 1988.) Cis/Trans-CTAC, two lots with purities of 90.2% and 94.85%, was administered dermally (6 hours/day, 5 days/week for 13 weeks) to clipped skin at doses of 0 (water vehicle control), 50, 200, or 1000 mg/kg bodyweight to 10 New Zealand White Rabbits per sex per dose. An area of approximately 400 cm^2 was clipped as needed. The application site was covered with gauze and cotton and held in place with a jacket. At the end of the exposure period, the area was wiped with a water-dampened towel. No systemic activity was reported, including body weight, hematology, clinical chemistry and ophthalmology. Slight to severe irritation of the treated skin was observed in animals in low, mid and high dose groups. The irritation appeared to be associated with abrasions resulting from the clipping process. The irritation was dose- related in terms of number of applications before irritation was noted and with

severity and incidence with fewer animals being affected at 50 mg/kg body weight than at the mid and high doses. Systemic NOEL = 1000 mg/kg. There was no NOEL for skin irritation. ACCEPTABLE. (Kishiyama and Gee, 3/21/03)

009 130006 Wright, P. A. "Subchronic 90-Day Dermal Toxicity." (Dow Chemical, 5/3/94) Cis/Trans CTAC (1-(3-chloroallyl)-3,5,7-triazo-1-azoniaadamantane chloride) (purity not stated) was given to B6C3F1 mice for 4- to 13- weeks. Doses of 0, 375, 750 or 1500 mg/kg were given 3 times a week to ten B6C3F1 mice/sex/group as 50 :l of an aqueous solution to clipped skin. The author claimed the mice were frequently grooming and apparently in the process, oral ingestion of the test article occurred. The unpalatability of the higher doses may have limited ingestion, making the differences between doses less. POSSIBLE ADVERSE EFFECTS were noted: Increased incidence in the vacuolation of portions of the forebrain and/or hippocampus in all treated groups with an increase in severity, centrilobular hypertrophy of the liver with increase in liver weight at all dose levels and clara cell hypertrophy of the lungs and trachea of treated animals. No NOEL. The results were presented in a three-page document and stated to be based on preliminary, unaudited results. The final report apparently is not on file. No work sheet. (Kishiyama and Gee, 3/20/03).

CHRONIC TOXICITY, DOG

no study submitted.

Subchronic, dog

007 038059 Schwetz, B. A., C. G. Humiston, G. C. Jersey, J. E. LeBeau and C. E. Wade "Dowicil® 100 antimicrobial: 90-day toxicity study in beagle dogs." (Toxicology Research Laboratory, Dow Chemical, 2/13/76 and supplement, 5/14/80) Dowicil 100 (lot 257736, 96.28% purity) was given in gelatin capsules at doses of 0, 7.5, 15 or 30 mg/kg/day, 7 days/week. In a preliminary study, 50 mg/kg resulted in vomiting. There were 4/sex/dose. Body weight, food consumption, hematology parameters, limited clinical chemistry and urinalysis were evaluated. Dogs were fasted overnight before termination. Brain, heart, liver, kidneys, adrenal glands and testes were weighed. Tissues of controls and high dose animals were examined with kidneys, liver, urinary bladder and bone marrow being examined for all groups. Ophthalmology was conducted pretest and at termination. There were no consistent effects on body weight or food consumption. There were slight differences in some hematological parameters at the high dose for males and at 15 and 30 mg/kg for females. Relative heart weight was lower at 15 and 30 mg/kg and liver weight was higher at 30 mg/kg. Changes were seen in the livers of dogs at 30 mg/kg/day and in 1/4 females at 15 mg/kg/day (obliterative vasculitis and perivasculitis of selected hepatic blood vessels). Other findings included hyperplasia of the reticuloendothelial cells lining the hepatic sinusoids and moderate perivascular and pericholangiolar mononuclear cell infiltration. One of 4 males at 30 mg/kg/day had necrosis and inflammation of the heart, possibly treatment-related, according to the authors. The supplement presented further data on the low level of protein in the urine, supplemental histology for spleen and heart for low and mid dose animals. Data presented for control males from other studies indicated that the 40 mg % protein in urine noted in one animal was not an uncommon finding as approximately 14% had values of 40 mg % or higher. For histology, sections of spleen and heart were made from stored tissues. All additional sections were reviewed as normal. NOEL = 7.5 mg/kg/day. UNACCEPTABLE, not upgradeable based on missing parameters. No adverse effect clearly identified. No worksheet. (Gee, 3/24/03)

-003 16322 Duplicate of 038059.

ONCOGENICITY, RAT

no study submitted.

ONCOGENICITY, MOUSE

no study submitted.

REPRODUCTION, RAT

no study submitted.

TERATOLOGY, RAT

**** 002 002626** John, J. A, J.H. Ouellette, and J. F. Quast. "Dowicil™ 200 - - Oral Teratology Study in Fischer 344 Rats." (Health and Environmental Sciences, Dow Chemical Company, HET-K-27342-(47), May 13, 1982.) Dowicil™ 200, purity 97.9%, was administered by gavage at doses of 0 (water), 5, 25, or 75 mg/kg/day to 34 or 35 mated Fischer 344 rats on days 6 through 15 of gestation. Maternal body weight was reduced slightly (7%) for high dose dams and body weight gain was also statistically lower for 25 mg/kg/day dams days 6 - 8 of gestation. Food and water consumption for high dose dams were reduced 6-31% and 14%, respectively and also, food consumption was slightly reduced (7%) for the mid dose group. Maternal NOEL = 5 mg/kg/day. The incidence of microphthalmia was increased to 17% and 19% for mid and high dose fetuses, respectively, compared with none in the control or low dose groups. Developmental NOEL = 5 mg/kg/day. **Possible adverse developmental effect.** (Keith Pfeifer (7/29/85) considered this study to be ACCEPTABLE.) One-liner and updated review by Kishiyama and Gee, 3/20/03.

-001 950715 Summary on the progress of 002 002626.

007 038062 John, J. A., T. K. Jeffries, B. H. Scortichini, N. M. Berdasco, and J. F. Quast. "Dowicil™ 200: Dermal Teratology Study in Rats." (Health and Environmental Sciences, Dow Chemical Co., HET K-27342-59, June 21, 1984.) Dowicil™ 200, purity 98.7%, cis isomer, was administered dermally at doses of 0, 250, or 500 mg/kg/day as a 50% aqueous solution in 0.1 or 0.2 mls to 25 mated female Fischer 344 rats during gestation days 6 through 15. The exposure area was clipped and occluded during exposure with an elastic gauze bandage secured with tape. It was stated that concentrations greater than 50% caused dermal irritation and that 0.2 ml was the largest volume that could be applied to the treatment area (not specifically stated but the nonabsorbent cotton was stated to be 2 in^2). Percent of body surface exposed was not given. Apparently the bandage was not removed during the study but the test material was applied under the cotton with a glass syringe. No treatment-related effects were reported. Maternal & Developmental NOEL = 500 mg/kg/day. UNACCEPTABLE (Only two dose levels in addition to the control; Insufficient information on test material application). Questionable if upgradeable. (Kishiyama and Gee, 3/25/03)

TERATOLOGY, RABBIT

no study submitted.

GENE MUTATION

**** 008 068709** Linscombe, V. A. and B. B. Gollapudi. "Evaluation of Cis/Trans-1-(3-

Chloroallyl)-3,5,7-Triaza-1-Azoniaadamantane Chloride in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay." (Lake Jackson Research Center, Dow Chemical Company, Laboratory Project Study ID TXT:K-027342-064, March, 1988.) Cis/trans-CTAC, purity 94.85 %, was evaluated *in vitro* for mutagenic potential at concentrations ranging from 16 to 125 :g/ml using Chinese hamster ovary cells in the absence and presence of rat liver activation. At the concentrations used, neither the pH nor the osmolality were affected. Treatment was for 4 hours. For cytotoxicity, three plates per culture were evaluated. After the eight-day expression period, five plates per culture were used for mutant frequency and for cloning efficiency. Without activation, results were negative. The number of TG^r Mutants/10^6 clonable cells averaged 31.2 (Assay #1) and 53.1(Assay #2) for Cis\Trans-CTAC at 125 :g/ml and was significantly greater than the control at 4.3 (assay #1) and 1.2 (assay #2) in the presence of activation. POSSIBLE ADVERSE EFFECT. The positive controls functioned as expected. ACCEPTABLE. (Kishiyama and Gee, 3/21/03).

007 038060 "Mutagenicity Test." (Raltech Scientific Services, Inc., RT No. 741925, August 6, 1979.) Dowicil* 200 preservative (purity not stated, lot 012690052) was evaluated for mutagenicity at concentrations of 0, 25, 50, 100, 250, or 500 :g/plate with and without metabolic activation (S9 Mix) using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, duplicate plates in a single trial. Numbers of revertants were not increased with test article with or without S9 Mix. Positive controls were functional. UNACCEPTABLE, major deficiencies. Not upgradeable. (Kishiyama and Gee, 3/24/03).

CHROMOSOME EFFECTS

** 008 068710 McClintock, M. L. and B. B. Gollapudi. " Evaluation of Cis/Trans-1-(3-Chloroallyl)-3,5,7-Triaza-1-Azoniaadamantane Chloride in the Mouse Bone Marrow Micronucleus Test." (Lake Jackson Research Center, Dow Chemical Company, Laboratory Project Study ID TXT:K-027342-062, March 1988.) Cis/trans-CTAC, purity 94.85%, was evaluated in the mouse bone marrow micronucleus test. The test article was administered via gavage at doses of 0 (water), 100, 333, and 1000 mg/kg to 5 CD-1 (ICR) BR mice/sex/group/sacrifice time (24 and 48 hours post-treatment). There were no mortalities reported. One thousand erythrocytes were evaluated per animal. Cis/trans-CTAC treatment did not significantly increase the number of micronucleated PCE's relative to the vehicle control under study conditions. The % PCE in the samples were comparable for all doses versus controls. ACCEPTABLE. (Kishiyama and Gee, 3/21/03).

DNA DAMAGE

007 038061 Domoradzki, J. Y. "The Evaluation of Dowicil 200 in the Rat Hepatocyte Unscheduled DNA Synthesis Assay." (Health and Environmental Sciences, Dow Chemical, HET K-27342-(44), March 28, 1981.) Dowicil 200, purity 96.3%, cis isomer, was evaluated for genotoxicity at concentrations ranging from 0.01 to 50000 :g/ml. Formaldehyde, 37% solution, was also evaluated at concentrations ranging from 0.0003 to 3000 :g/ml using primary hepatocytes from a male Fischer 344 rat. Incubation was for 18 hours in the presence of radioactive thymidine. Net nuclear grains were scored for 15 cells on each of two coverslips. Neither of the test articles induced DNA repair. UNACCEPTABLE. Not upgradeable (inadequate number of cells were scored). (Kishiyama and Gee, 3/24/03).

** 008 068711 Gollapudi, B. B. and M. L. McClintock. "Evaluation of Cis/Trans-1-(3-Chloroallyl)-3,5,7-Triaza-1-Azoniaadamantane Chloride in the Rat Hepatocyte Unscheduled DNA Synthesis (UDS) Assay." (Lake Jackson Research Center, Dow Chemical Company, Laboratory Project Study ID TXT:K-027342-063, March 1988.) Cis/trans-CTAC, purity 94.85%,

was evaluated in the rat hepatocyte unscheduled DNA synthesis (UDS) assay at concentrations from 1.0 to 100.0 :g/ml. Incubation was for approximately 18 hours in the presence of tritiated thymidine. Cis/trans CTAC treatment did not elicit a positive UDS response in the rat hepatocyte cultures. Positive controls were functional. ACCEPTABLE. (Kishiyama and Gee, 3/24/03)

** 50276 - 013 202567 Cifone, M. A. "*In vivo/in vitro* unscheduled DNA synthesis in rat primary hepatocyte cultures at two timepoints with a dose rangefinding assay with Cis CTAC." (Covance, Study No. 22655-0-494OECD, Dow No. 011119, January 25, 2002) Cis-CTAC (Dowicil 150, 98.7%, lot no. NE2801QT1P) was given to male Fischer 344 rats by oral gavage at doses of 0 (water), 750 or 1500 mg/kg. The doses were based on a rangefinding study that tested doses of 500, 1000, 1500, 1750 and 2000 mg/kg, 3/sex/dose. Mortality occurred at 1750 and 2000 mg/kg. In the UDS assay, males were sacrificed at 2 - 4 and 14 - 16 hours after dosing. Hepatocytes were isolated and put into culture. After attachment, they were incubated with ^{3}H-thymidine for 4 hours and for an additional 16 to 20 hours with 0.25 mM thymidine before preparation for autoradiography. Dimethylnitrosamine was given ip as the positive control and was functional. There was no indication of the induction of UDS at either dose or harvest time. No adverse effect. ACCEPTABLE study. (Gee, 3/25/03)

OTHER

008 068712 Rondon, N. G. and Hayden, A. C. "A comparison of the isomers of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride." (Central Research Department, Dow Chemical, report ES-704R, may 11, 1987) Comparing charge distribution, molecular geometry and molecular orbitals, the authors concluded that the Cis and trans isomers are very similar. No worksheet. (Gee, 3/24/03).

003 016320 Norris, J. M., J. Bourne and G. Sparschu "25-Day repeated dermal toxicity study on Dowicil® 100 preservative with and without 25% of sodium bicarbonate." (Dow Chemical, June 3, 1970) Dowicil 100 (60/40 mixture of cis and trans isomers, lot #02707(A)) and a sample containing 25% sodium bicarbonate (XD-1840L) was applied to the clipped skin of New Zealand albino rabbits. There were 2/sex/dose group given aqueous solutions of 0.5, 1.0 or 2.0%, equivalent to 25, 50 or 100 mg/kg for a 3 kg rabbit in 15 ml. Six per sex served as controls. The area of application was 4 inches square and approximately 15% of the body surface. Forty-eight hours passed before the first application to allow for healing of minor lesions from clipping. Applications were made 5 days per week for 3 ½ weeks for a total of 18 exposures. A gauze pad was soaked with the 15 ml of test solution, placed over the clipped area and taped to marginal hair. The gauze was kept moist during the 6 hour exposure by adding additional water. At the end of the exposure period, the pad was removed and the area washed with ivory liquid and dried. Animals apparently were held in stocks during exposure. Dermal response was observed each day before treatment. Some hematology and clinical chemistry parameters were evaluated as well as selected organ weights (heart, kidneys, spleen, liver, testes and brain). The report states that no skin responses were observed in any group. There were no findings in hematology, clinical chemistry or organ weights that were related to treatment. No adverse effects. UNACCEPTABLE (insufficient number of animals per group, dose selection not justified, test site not occluded, incomplete clinical chemistry, others). Not upgradeable. No worksheet. (Gee, 3/26/03)